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Frank-Starling law of the heart and the cellular mechanisms of length-dependent activation

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About a century ago, Otto Frank in Germany and Ernest Starling in England reported on the relationship between the extent of ventricular filling and pump function of the heart, a phenomenon collectively referred to as Frank-Starling's Law of the Heart. Frank's experiments employed the isolated frog heart and suggested that maximum ventricular pressure critically depends on whether the heart is operating under ejecting or isovolumic conditions [10]. That is, ejection appeared to deactivate cardiac contraction. Starling's experiments [31], using a isolated canine heart-lung preparation, showed that cardiac output was directly proportional to filling pressure and, thus, ventricular volume and independent of peripheral resistance: "... the larger the diastolic volume of the heart... the greater is the energy of its contraction." More recently, Suga and Sagawa proposed a time-varying elastance model to describe ventricular contractile function [35]. These investigators demonstrated, in the isolated canine heart, a direct and proportional relationship between end-systolic pressure and end-systolic volume; this phenomenon has since been confirmed in many species, including human. As illustrated in Fig. 1A, the end-systolic pressure-volume relationship was found to be independent of loading conditions, but critically dependent on contractile state (dashed line). Apart from predicting ventricular stroke volume under a variety of loading conditions, the time varying elastance model similarly provides a framework to predict myocardial oxygen consumption [35].

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Both Frank and Starling understood that their data bore a direct similarity to the variation of active force development in skeletal muscle as function of muscle length [3], thereby linking ventricular function to a fundamental property of cardiac muscle. Indeed, twitch force in isolated cardiac muscle has been shown to be directly proportional to systolic sarcomere length [21]. Furthermore, the shape of the relationship is modulated by contractile state such that more force is generated at a given sarcomere length when contractile activation is elevated (illustrated in Fig. 1B) [21]. What cellular mechanisms might underlie this phenomenon? At first sight, it may appear logical to suggest that variation of contractile filament overlap underlies the Frank-Starling Law of the Heart (described further below and in Fig. 2). However, the relationship between contractile force and sarcomere length is far too steep and to variable between contractile states (Fig. 1B) to be solely explained by such a simple mechanism [1,20, 21].

The contractile apparatus is activated by calcium ions that are released by the sarcoplasmic reticulum upon activation. Early experiments by Fabiato suggested that the released amount of this activator calcium varied with sarcomere length [8], but these results have not since been confirmed. More recent experiments [7,17, 20] clearly demonstrated that it is the level of activation of the cardiac contractile apparatus itself that is sensitive to changes in sarcomere length (Fig. 1C). These experiments were performed on chemically permeabilized (skinned) isolated cardiac muscle, a preparation that allows direct access to the contractile apparatus such that steady state force can be measured as function of activator calcium concentration. Thus, as is illustrated in Fig. 1C, there is a direct proportionality between sarcomere length and the sensitivity to calcium ions of the cardiac sarcomere, such that more force is generated at a given concentration of activator calcium as sarcomere length is increased (the curves are shifted to the left on the [activator calcium] axes at higher sarcomere length). Hence, it can be said that the sarcomere possesses a length dependent activation property. It should be noted that intact twitching

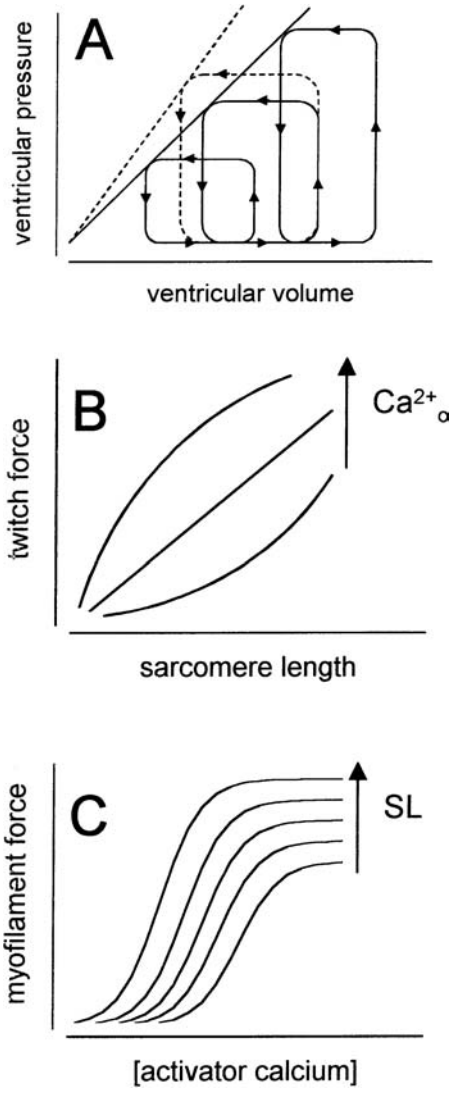

Fig. 1A–C Frank-Starling's Law of the heart: relation to length dependency of myofilament length activation. **A** Schematic illustration of ventricular pressure-volume loops as measured by Suga and Sagawa in the isolated canine heart [35]. End-systolic pressure is uniquely determined by end-systolic volume and independent of ventricular loading conditions. The end-systolic pressure-volume relationship is sensitive to contractile state: here, the dashed line indicates an increased level of inotropy, resulting in increased ejection volume and increased end-systolic pressure for a given amount of ventricular filling (dashed pressure-volume loop). **B** Schematic illustration of the relationship between peak twitch force and systolic sarcomere length in isolated cardiac muscle. An increase in contractile state, in this case increased concentration of Ca^{2+} in the bathing medium, results both in an elevation of the peak twitch force-sarcomere length relationship as well as a change in the shape of this relationship: for a given end-systolic sarcomere length, peak twitch force is increased [20, 21]. **C** Schematic illustration of the relationship between activator calcium concentration and myofilament force generation [7, 17, 20]. Increases in sarcomere length (*SL*) induce an increase in maximum, calcium saturated myofilament force generation as well as an increase in calcium sensitivity. The latter is manifest as a leftward shift of the entire force-calcium relationship. Myofilament activation is cooperative, meaning that myofilament force generation occurs over a narrow range of activator calcium concentration (steep activation curve). The level of cooperativity, in contrast to maximum calcium saturated force and calcium sensitivity, appears not to depend on sarcomere length [7]

cardiac muscle responds to a change in length in two distinct phases: an immediate change in twitch force, and a slower phase that develops over the course of several minutes. There is good evidence to suggest that the latter phase is due to a change in sarcoplasmic reticulum calcium release secondary to altered calcium loading of the cell, while the immediate response is due to the change in calcium sensitivity of the cardiac sarcomere described above [1].

Despite the importance for the Frank-Starling mechanism, the molecular mechanisms that underlie the immediate response of myofilament force generation upon a change in sarcomere length have not been entirely elucidated. The change in myofilament force upon variation of sarcomere length appears to be due to a change in the number of active cycling, force producing cross-bridges in the cardiac sarcomere [1, 40, 41]. The top panel of Fig. 2 shows a schematic illustration of the proteins present in the sarcomere of striated muscle. Dimers of the asymmetric molecule myosin are linked by their tail portions to form the backbone of the thick filament, while the globular heads of myosin protrude from the thick filament (M; blue). These globular heads, or cross-bridges, are believed to cyclically attach to the actin filament (A; orange) [18]. When strongly-bound, the cross-bridges produce a pulling force on actin and, through the thin filament, on the proteins that make up the Z-band (Z; gray). The Z-bands are mechanically coupled via a multitude of proteins that include the integrin receptors at the cell surface to the extracellular collagen network, thus transmitting actin-myosin produced force to the tendons in skeletal muscle or towards the heart's cavity in the heart so as to produce pressure. Recently, an additional sarcomeric protein has been identified, titin, a high molecular weight giant protein that spans the entire half sarcomere from the Z-band to the M-line and binds tightly with the myosin thick filament (T; red) [15, 26, 39]. Striated muscle contraction is regulated by the heteromeric protein complex troponin and the tropomyosin filament, both located on the thin filament (note: not shown in Fig. 2) [38]. Troponin is composed of troponin-C (TnC), the calcium receptor; troponin-I (TnI), an inhibitor of contraction; and troponin-T (TnT), a tropomyosin binding protein. There is good evidence to suggest that calcium binding to TnC results in the movement of tropomyosin away from myosin binding sites on actin, thereby allowing cross-bridge formation and active force development [18, 24]. It is important to note that all striated muscle (skeletal and cardiac) are fundamentally identical in terms of the type of proteins that make up the sarcomere, but differ in terms of the specific isoforms expression of these proteins (which usually derive from different gene products in different muscle types). One important difference between skeletal and cardiac muscle is the magnitude of length dependent activation, being larger in cardiac than in skeletal muscle [2, 8, 22]. Fast skeletal muscle expresses a specific form of TnC that is distinct from cardiac TnC. Early experiments by Gulati and Babu employing TnC exchange in

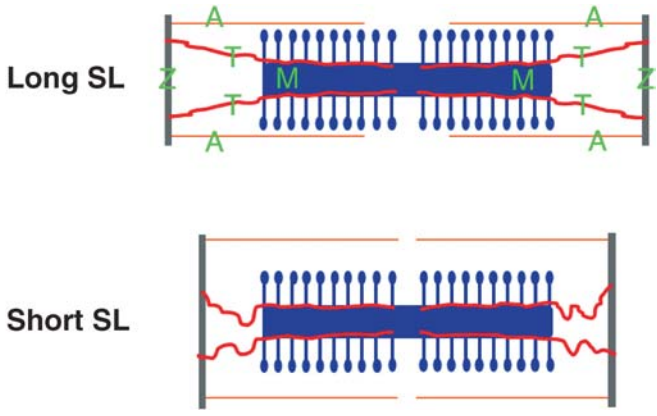

Fig. 2 Schematic illustration of sarcomeric structure in striated muscle. The thick filament is composed of myosin, the globular heads of which protrude from the thick filament (*M*; blue). Myosin heads interact with the actin filament (*A*; orange) to form cross-bridges. The cross-bridge pulling force on actin is transmitted mechanically to the Z-band (*Z*; gray). Titin, a high-molecular-weight protein, is shown to span the entire half sarcomere from the Z-band and onto the myosin thick filament (*T*; red). The *top panel* shows a long sarcomere length (*SL*), while the bottom panel shows a short SL. The inter-filament spacing hypothesis of length dependent activation is based on the proposition that variation in SL causes a concomitant change in the distance between the thick and thin filament which, in turn, induces a change in the reactivity of the myosin heads (*blue dots*) for actin (*orange filament*). An alternative theory proposes that mechanical strain on titin (*red*) induced by stretch of the sarcomere (*see top panel*) affects the reactivity of the myosin heads either due to a direct effect of titin strain on inter-filament spacing, or due to altered thick or thin filament structure. Note that for clarity, the sarcomere lengths depicted in this figure to illustrate the myofilament lattice spacing hypothesis are longer than those that may occur in the heart; under physiological conditions, cardiac sarcomeres operate largely at a length where there is an overlap between opposing actin filaments (double overlap)

either fast skeletal or cardiac muscle indicated that the specific isoform of TnC alone was sufficient to impart the corresponding length dependent property on that muscle type [2]. Hence, those experiments suggested that TnC might comprise a pivotal component of the length sensing entity in striated muscle. However, more recent detailed experiments by the Moss group have rendered this possibility less likely [29].

A unifying theory that has gained acceptance during the last decade proposes that the impact of sarcomere length on myofilament calcium sensitivity (Fig. 1C) is due to changes in the spacing between the thick and thin filaments [11, 14, 28]. This theory is schematically illustrated in Fig. 2. Because myofibrils maintain close to constant volume [19, 34], elongation of the sarcomere is expected to lead to a reduction of the distance between the thick and thin filaments (compare top and bottom panel). A closer approximation of the myosin heads to actin may be expected to increase the probability of strong cross-bridge formation at a given concentration of activator calcium. Thus, one would predict an increase in myofilament calcium sensitivity at the higher sarcomere length (top panel of Fig. 2). Several experiments have provided support for this theory. Osmotic compression of the myofilaments by high-molecular-weight molecules that cannot enter the myofilament lattice structure, such as dextran, induces an increase in myofilament calcium sensitivity concomitant with a reduction of muscle diameter [11, 14, 28]. Since it has been shown that a reduction in muscle diameter occurs in parallel to a reduction in myofilament lattice spacing in skeletal muscle [27], the increase in myofilament calcium sensitivity following dextran treatment without a change in sarcomere length is consistent with the myofilament lattice spacing theory. More direct support was provided by Fuchs and co-workers, who showed that myofilament calcium sensitivity could be rendered length independent when muscle diameter was kept constant by applying an appropriate amount of dextran at each sarcomere length studied [11]. A similar result was obtained by McDonald and co-workers, who showed in single permeabilized cardiac myocytes that application of dextran at a short sarcomere length was sufficient to increase myofilament calcium sensitivity to match that recorded at the high sarcomere length, despite the fact that sarcomere length had not changed [28].

We have recently reexamined the dextran approach, this time employing X-ray diffraction to directly measure myofilament lattice spacing. As illustrated in Fig. 3A, we found in cardiac muscle that application of dextran reduced muscle diameter to a greater extent than myofilament lattice spacing, particularly at short sarcomere lengths [23]. Also apparent from these data is that application of 3% dextran compressed the myofilament lattice to a far greater extent than stretching the sarcomeres in the absence of dextran. Thus, to match myofilament lattice spacing at a short sarcomere length, only 1% dextran was required as opposed to the 3–5% dextran used in the earlier studies that relied on muscle diameter or changes in calcium sensitivity. Unexpectedly, 1% dextran was found not to affect myofilament calcium sensitivity, even though myofilament lattice spacing was reduced to a similar extent as that induced by a change in sarcomere length; increasing sarcomere length, on the other hand, did indeed increase myofilament calcium sensitivity, precisely as expected (Fig. 3B). Consistent with the previous studies, we did indeed find that application of higher concentrations of dextran (3% or 6%) increased myofilament calcium sensitivity. Hence, the earlier observations linking muscle diameter to myofilament calcium sensitivity may have been a fortuitous finding, caused perhaps by an independent effect of higher concentrations of dextran on myofilament calcium sensitivity, rather than showing a direct causal connection between myofilament spacing and myofilament calcium sensitivity. In support of this notion, we recently found in another study comparing fast and slow skeletal muscle of the rat, no differences in myofilament lattice spacing as a function of sarcomere length, despite the fact that the length dependent properties of these two muscle types are vastly different [22]. Elucidation which specific thick or thin filament protein component is responsible for this

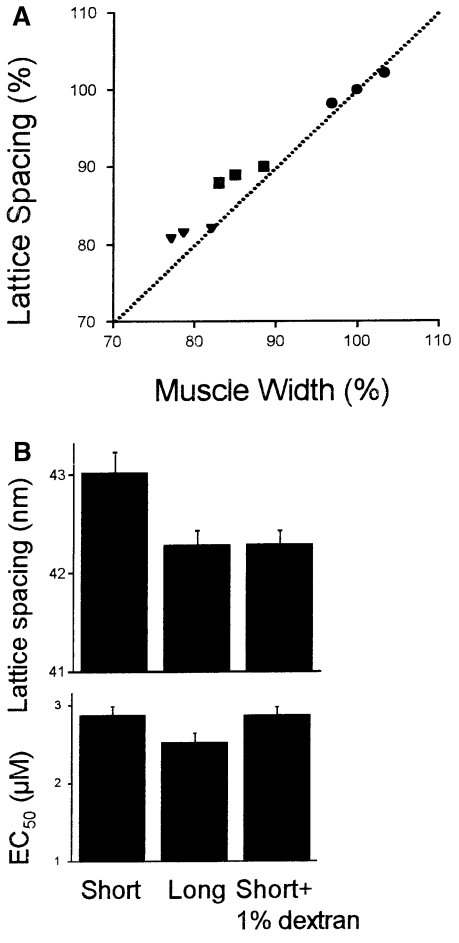

Fig. 3A,B Myofilament lattice spacing and Ca^{2+} sensitivity. **A** Relationship measured in isolated skinned rat cardiac muscle between the width of the muscle and myofilament lattice spacing as measured by X-ray diffraction [19]. Muscles were studied at 3 levels of sarcomere stretch (1.95 μm, 2.10 μm, and 2.25 μm) in the presence of dextran at 0% (*circles*), 3% (*squares*), and 6% (*triangles*). Stretch of the cardiac sarcomere resulted in a proportional reduction in myofilament lattice spacing and muscle width in the absence of myofilament compression by dextran only (*circles*). In contrast, under conditions of dextran compression, sarcomere stretch resulted in a proportional reduction of muscle width, but not in myofilament lattice spacing. In addition, application of 3% dextran induced compression of the myofilament lattice to a greater extent that sarcomere stretch in the absence of dextran (*compare circles and squares and dashed line of identity*). Modified from Konhilas et al. [23]. **B** *Upper bar graphs* show myofilament lattice spacing as measured by X-ray diffraction in isolated skinned rat cardiac muscle at a short sarcomere length (*Short*: 2.02 μm), long sarcomere length (*Long*: 2.10 μm), and at the short sarcomere length in the presence of 1% dextran (*Short+1% dextran*: 2.02 μm). Application of 1% dextran at the short sarcomere length was sufficient to match myofilament lattice spacing at the long sarcomere length in the absence of dextran. The *lower bar graphs* show the values for myofilament calcium sensitivity measured under these corresponding conditions. Length-dependent activation of the cardiac sarcomere is apparent by the reduction in EC_{50} in the absence of dextran upon stretch to the long sarcomere length. However, myofilament calcium sensitivity was not affected by application of 1% dextran at the short sarcomere length, despite the identical reduction in myofilament lattice spacing. These data suggest that myofilament lattice spacing may not underlie the molecular mechanism of length dependent activation in the heart. Modified from Konhilas et al. [23]

difference in length dependent activation will await further study. As a caveat, it should be noted that our conclusions, and those of others, are based entirely on measurements of either muscle diameter or myofilament spacing in relaxed, non-contracting muscle preparations. It is very likely that the myofilament lattice rearranges during contraction, the very condition that exist when myofilament calcium sensitivity is assessed.

If myofilament lattice spacing does not play a prominent role in length-dependent activation of striated muscle, then what other molecular mechanism may be involved? Myofilament activation is highly cooperative, i.e., force development increases steeply over a very narrow concentration range of activator calcium (see Fig. 1C) [1, 4, 7, 9, 17, 20, 33, 38]. Cooperative myofilament activation may be due to enhanced probability of calcium binding to TnC, either when neighboring TnC sites are occupied by calcium or when proximate cross-bridges are bound to actin, or due to promotion of further cross-bridge formation by near-neighbor actively cycling cross-bridges [4, 33]. Regardless of the underlying mechanism, there appears to be a linkage between the extent of cooperative activation and length dependent activation. First, manipulation of cooperative activation by various agents or substrates also affects length dependent activation [9, 12, 13, 36]. Second, in comparing various striated muscle types, we recently found a correlation between the level of cooperativity and length dependent activation among fast, slow, and cardiac muscle of the rat [22]. However, although strong cooperative interaction may be a prerequisite for length-dependent activation, cooperative activation itself does not appear to be length dependent, as we have recently shown in chemically permeabilized rat myocardium [7]. Thus, the precise role of cooperative activation in length dependent activation is, at best, incompletely understood.

Another potential mechanism for length dependent activation that has recently been proposed involves the giant cytoskelelal protein titin. Titin is well positioned within the sarcomere to take on the role of length sensor, since the protein spans the space between the Z-line and the center of the sarcomere (Fig. 2) [15]. The protein plays an important role in the generation of passive muscle stiffness originating from within the sarcomere [15, 16, 25]. Furthermore, titin is known to possess binding sites for both actin and myosin [15, 37]. Indeed, recent results have suggested that either selective removal of titin by partial protein digestion or reduction of mechanical strain on titin, reduces the length dependent property of skinned cardiac muscle [5]. Titin's action could be due either to a direct effect on myofilament lattice spacing [5], a possibility rendered less likely in light of our recent results [23], or due to a direct effect of titin strain on cross-bridge reactivity (via its interaction with actin or myosin) [23]. Finally, another potential mechanism underlying length dependent activation, at least in cardiac muscle, may simply be a reduction in the number of potential cross-bridges that can be formed at short sarcomere length due to the (double) overlap

between opposing actin filaments. Recent mathematical modeling by us has shown that this proposition may be feasible (J.J. Rice, G Stolovitzky, Y Tu, and PP de Tombe, unpublished observations). One problem with this proposal, however, is the fact that calcium sensitivity increases in skeletal muscle well beyond thick and thin filament overlap on the descending limb of the force-sarcomere length relationship (i.e., a condition, also, of diminished cross-bridge numbers but now associated with increased calcium sensitivity rather than reduced calcium sensitivity as in cardiac muscle at short sarcomere length).

In conclusion, Frank-Starling's Law of the heart describes an important and fundamental integrated cardiovascular regulatory principle. At its basis, it is caused by a change in myofilament sensitivity to activator calcium upon a change in sarcomere length. Although the deciphering of its molecular mechanism is currently pursued vigorously in various laboratories, a definitive answer has yet to be produced. Powerful techniques for study of structure-function relationships are at our disposal. These range from X-ray diffraction that allow examination of thick and thin filament structure [30], to the expression and purification of recombinant (mutant) protein that can be exchanged into skinned striated muscle preparations [6] and transgenic animal models [38]. Elucidation of the Frank-Starling mechanism undoubtedly will provide further insights into the complex protein regulatory system of muscle contraction. However, at the same time, and perhaps even more importantly, it will also provide for an elegant and necessary connection between the "old" science of systems physiology that was practiced by Frank and Starling about a century ago, and that of the "modern" science of functional genomics of today [32].

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